OA09.05

Structure of a CH58-like V2 Antibody from Natural Infection Reveals Convergent Heavy Chain Maturation and a Novel K169 Binding Light Chain Motif

Constantinos Kurt Wibmer[1,2], Charmaine van Eeden[1,2], Balakrishnan Vijayakumar[2], Nonhlanhla N. Mkhize[1,2], Bronwen E. Lambson[1], Salim S. Abdool Karim[3], Manuel Fernandes[2], Yasien Sayed[2], Penny L. Moore[1,2,3], Lynn Morris[1,2,3]

[1]National Institute for Communicable Diseases (NHLS), South Africa, [2]University of the Witwatersrand, South Africa, [3]University of KwaZulu-Natal, South Africa

Background: K169-dependent V2 binding antibodies were a correlate of reduced infection risk in RV144. CH58, a V2-specific antibody isolated from one vaccinee competed with α4β7, and used a key light chain encoded CDRL2 ED-motif to bind K168/K169. Here we determine the structure of a V2/K169 reactive antibody isolated from CAPRISA donor CAP228 (CAP228-16H) bound to a V2 peptide, and compare this to CH58.
Methods: Complexes were screened for crystal growth across 396 conditions. The structure was solved using Phenix/Coot, and interactions were weighted by mutagenesis and ELISA. Longitudinal deep sequencing of CAP228-16H immunoglobulin variable regions was used to trace specific maturation pathways.
Results: Optimised crystals diffracted to 2.4Å in $P2_12_12_1$. The V2 conformation in both CH58 and CAP228-16H bound structures was strikingly similar, with residues 166-176 adopting an α helix and residues 177-182 an extended coil. CAP228-16H was derived from the same VH5-51 gene as CH58, and shared germline encoded contacts between its anionic CDRH2 and K/R178 in V2. Deep sequencing of CAP228-16H identified similar pathways of affinity maturation in the CDRH1 of both antibodies that formed a key salt bridge with residue D180 in the α4β7 binding motif. Only CDRH3 interactions between the two antibodies differed, in that CAP228-16H preferred Y173 over H173, and made contacts with Y177 that allowed for tyrosine sulfation, likely to occur in natural infection. CAP228-16H used a VL3-21 gene that does not encode the signature ED-motif, but still forms key V2 interactions with K168 and K169 via an anionic pocket formed by the germline CDRL2 DDSD-motif.
Conclusions: By solving the CAP228-16H crystal structure we identify V2-interacting signatures in the VH5-51 CDRH2, as well as two identical maturation pathways used by CAP228-16H and CH58 to contact the α4β7 binding motif. The use of VL3-21 identifies a new CDRL2 motif able to recognise K168/K169, broadening the light chain germline repertoire used by RV144-like V2 antibodies.

OA09.06LB

Structure of a Natively-glycosylated HIV-1 Env Reveals a New Mode for VH1-2 Antibody Recognition of the CD4 Binding Site Relevant to Vaccine Design

Harry Gristick[1], Lotta von Boehmer[2], Anthony West Jr.[1], Michael Schamber[1], Anna Gazumyan[2], Jovana Golijanin[2], Michael Seaman[3], Gerd Fätkenheuer[4], Florian Klein[4], Michel Nussenzweig[2], Pamela Bjorkman[1]

[1]Caltech, United States, [2]Rockefeller University, United States, [3]Beth Israel Deaconess Medical Center, Harvard Medical School, United States, [4]German Center for Infection Research (DZIF), Germany

Background: Structural studies of broadly neutralizing antibodies (bNAbs) bound to Env trimers have revealed mechanisms by which bNAbs targeting various epitopes penetrate the glycan shield to either accommodate or include *N*-glycans in their epitopes. Although accessibility to the conserved host receptor (CD4) binding site (CD4bs) is restricted by surrounding glycans, VRC01-class bNAbs mimic CD4 binding to share a common mode of gp120 binding and glycan accommodation using a VH1-2*02-derived variable heavy (V_H) domain. While attractive candidates for immunogen design, features of VRC01-class bNAbs such as a high degree of somatic hypermutation (SHM) and a short (5-residue) light chain (LC) complementarity determining region 3 (CDRL3) (found in only 1% of human LCs) suggest they might be difficult to elicit through vaccination. However, we recently isolated a VH1-2*02-derived CD4bs bNAb, named IOMA, that includes a normal-length (8 residues) CDRL3.
Methods: We used X-ray crystallography to solve the first structure of a fully- and natively-glycosylated Env trimer in complex with IOMA, and the V3-loop-directed bNAb 10-1074.
Results: Our structure revealed antibody-vulnerable glycan holes and roles of complex-type *N*-glycans on Env that are relevant to vaccine design, while also demonstrating that IOMA is a new class of CD4-mimetic bNAb that contains features of both VH1-2/VRC01-class and VH1-46/8ANC131-class bNAbs.
Conclusions: Analysis of the native glycan shield on HIV-1 Env allows the first full description of the interplay between heterogeneous untrimmed high-mannose and complex-type *N*-glycans within the CD4bs, V3-loop, and other epitopes on Env. In addition, the structural characterization of IOMA revealed an alternative pathway from VRC01-class bNAbs relevant to vaccine design, which could more readily lead to an effective vaccine response due to higher frequencies of normal-length CDRL3s compared with the rare 5-residue CDRL3s required for VRC01-class bNAbs, and a lower need for SHMs.